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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,621	09/07/2005	Yuko Kiyosue	082368-002400US	3690

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,621	KIYOSUE ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/22/05,8/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Restriction Requirement:

Applicant's election, without traverse of Group II, claims 5-10, drawn a polynucleotide that encodes a mutant APC protein, in the reply filed on 14 May 2007 in response to Office Action of 13 April 2007 is acknowledged. In response to requirement for species election, applicant elected Species C, C-terminal amino acid region starting from amino acid position 860 in the APC protein of SEQ ID NO:1.

Claims 5-10, 13-15 are pending in the instant application. Claim 5 has been amended and the amendment made of record. Claims 13-15 have been have been newly submitted, and the submission made of record. Claims 5-10 and 13-15 are under consideration.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 22 February 2005 and 2 August 2006 have been considered. Signed copy is attached.

Objections

Claims:

Claim 15 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to the claims from which it depends in the alternative only. See MPEP § 608.01(n). Appropriate correction is required.

Claim 13 is objected to as encompassing non-elected inventions. Appropriate correction is required.

Rejections

35 U.S.C. § 101:

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5-9, and 13-15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 5-9, and 13-15 are directed to polynucleotides encoding mutant APC proteins. The claims, as written does not sufficiently distinguish over a polynucleotide encoding a mutated polypeptide that naturally exists in cells because the claims do not particularly point out any non-naturally occurring differences between the claimed sequences and naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. (See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of language indicating an "isolated" polynucleotide (See MPEP 2105).

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-10 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague and indefinite in reciting "APC". The claim should recite the full name of the protein the first time it is recited. Furthermore, the claim is indefinite in reciting "comprising the function....". A compound cannot "comprise" a function. It is

unclear if applicant intends a polynucleotide that comprises the biological activity, or intends a protein that comprises the biological activity.

Claims 8, 9, and 14 are vague and indefinite in reciting "derived from". It is unclear if applicant is referring to material isolated from the recited mammal or amphibian, or material from said mammal or amphibian that has been altered.

Claim 13 is vague and indefinite in reciting "at least any one". It is unclear if applicant intends the scope to include other deletions in addition to ones recited in sections a-c.

Claim 15 is vague and indefinite in reciting "one or more amino acids are substituted, deleted added and/or inserted". There is no upper limit to the number of amino acids which may by substituted, deleted, added and/or inserted. Thus, it is unclear if applicant intends the scope to include changes over the entire amino acid sequence or, for example, deletion of the entire sequence.

Claims 6, 7 and 10 are included in this rejection as being dependent from a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10, 14 and 15 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide that encodes a mutant APC protein wherein the protein consists of SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2827-2829 of SEQ ID NO:1, SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2159-2829 of SEQ ID or SEQ ID NO:1 with a deletion of amino acid residues 860-2829, does not reasonably provide enablement for a polynucleotide that encodes <u>any</u> mutant APC, or a mutant APC protein in which one or more amino acids are substituted, deleted added and/or

inserted. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims: Claims 5 and 15 are broadly drawn to a polynucleotide that encodes a mutant APC protein (Claim 5) in which one or more amino acids are substituted, deleted, added, and/or inserted (Claim 15). Claim 13 recites a polynucleotide which encodes a protein wherein deletions occur at the C-terminal portion of the molecule.

The specification teaches: The term "mutant" refers to a protein comprising the amino acid sequence of a normal APC protein, in which one or more amino acids have been substituted, deleted, added, or inserted. ....That is, the types of mutations present in the mutant APCs of this invention are not particularly limited, as long as they have the function of inducing piling up of cells [paragraph 0032 in PGPUB 20060100418, the PGPUB of the instant invention]. The mutant APCs of this invention are not limited to specific types of APC mutants. An example of the mutant APCs of this invention is a mutant of the Xenopus laevis APC protein comprising the amino acid sequence of SEQ ID NO: 1 [paragraph 0034]. In a preferred embodiment of the present invention, the mutant APCs are proteins in which a portion of the amino acid region of a normal APC has been deleted (truncated APC proteins) [paragraph 0035]. The mutant APCs of this invention are normally proteins in which the three amino acids of a TSV sequence (DLG-binding region) at the C-terminus are deleted [paragraph 0036]. The disclosure specifically teaches APC mutant proteins in which the protein consists of SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2827-2829 of SEQ ID NO:1, SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues

2159-2829 of SEQ ID or SEQ ID NO:1 with a deletion of amino acid residues 860-22829 (figure 1). Thus, the claims are broadly drawn to polynucleotides encoding an unlimited variety of mutant proteins, but an enabling disclosure is provided only for polynucleotides encoding APC mutant proteins in which the protein consists of SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2827-2829 of SEQ ID NO:1, SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2159-2829 of SEQ ID or SEQ ID NO:1 with a deletion of amino acid residues 860-22829.

The working examples: The working examples teach the production of polynucleotides encoding mutant proteins of in which the protein consists of SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2827-2829 of SEQ ID NO:1, SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2159-2829 of SEQ ID or SEQ ID NO:1 with a deletion of amino acid residues 860-22829 and transfection of cells with said polynucleotides (figure 1 and Examples 1-7). There are no examples, working or prophetic of polynucleotides encoding mutant polypeptides with other amino acid substitutions, deletions, additions, and/or insertions.

The art teaches: The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 491-495). However, Applicant has provided little guidance beyond the presentation of sequence data and general recitation of

substitutions, deletions, additions, and/or insertions to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions, other than the specifically recited truncation mutants. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site or the domain of the protein responsible for the activity of "inducing piling up of cells" were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite sufficient structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 5-10, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides encoding mutant proteins in which one or more amino acids are substituted, deleted, added and/or inserted. The claims do not require that the polypeptide possess any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by functional characteristic, encoding a polypeptide that has the biological activity of "inducing piling up of cells".

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a recitation of a functional limitation, that is encoding a polypeptide that has the biological activity of "inducing piling up of cells". There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polynucleotides encoding APC mutant proteins in which the protein consists of SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2827-2829 of SEQ ID NO:1, SEQ ID NO:1 with a deletion of the C-terminal region of amino acid residues 2159-2829 of SEQ ID or SEQ ID NO:1 with a deletion of amino acid residues 860-22829 but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5-7, 9, 10, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Mimori-Kiyosue et al. (2000. J Cell Biol 148:505-517, cited on IDS of 22 February 2005, reference AO). Mimori-Kiyosue et al teach a deletion mutant of *Xenopus* APC (abstract); the reference teaches that truncation mutants (of the COOH-

terminal region) of the APC protein caused accumulation of enterocytes near the crypt-villus transition (page 506, 1st column, 2nd paragraph). The reference teaches construction of expression vectors with polynucleotides encoding the mutant protein (page 506, 2nd column 3-4 paragraphs) and transfection of cells with cDNAs encoding the mutant protein into culture *Xenopus* A6 epithelial cells (page 506, 2nd column, 5th paragraph, page 512, 2nd column, last paragraph bridging page 513). Thus, the teachings of Mimori-Kiyosue et al. anticipate all the limitations of claims 5-7, 9, 10, 14 and 15.

Claims 5-8, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Oshima et al. (1995. PNAS 92:4482-4486, cited on IDS of 22 February 2005, reference AS). Oshima et al. teach a mutated gene (polynucleotide) encoding a mutant mouse APC which is truncated at amino acid 716 and contructing mice that contained a mutant gene encoding the mutant polypeptide; the mice developed multiple polyps throughout the intestinal tract (abstract). The reference teaches production of vectors, electroporating ES cells and using the cells to generate chimeras and mouse embryos comprising polynucleotides encoding the mutant protein (page 4482, 2nd column, 2nd and 3rd paragraphs).

Claims 5-8, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (1994. Cancer Res. 54:3672-3675). Smith et al. teaches an expression vector comprising a polynucleotide encoding a mutant APC protein which has a 5-base pair deletion and is the most frequent mutation found in FAP patients (page 3672, 2nd column, 2nd paragraph), thus anticipating the limitations of claims 5, 6, and 15. The reference teaches transfection of human colorectal cancer cell line, RKO and the mouse fibroblast cell line, NIH3T3 with the above expression vector (page 3672, 2nd column, 3rd and 4th paragraph) thereby anticipating the limitations of claims 7 and 8. Thus, Smith et al teach and anticipate all the limitations of Claims 5-8, 10, and 15.

Claims 5 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Su et al. (1992. Science 256:668-670). Su et al. teaches a mutation in mouse APC gene (Min phenotype) which is a fully penetrant autosomal dominant trait. Min mice develop numerous adenomas throughout their intestinal tract (page 668, 1st column, 2nd paragraph). The reference teaches polynucleotide that encodes the mutant APC (page 256, 3rd column (3rd paragraph). A transversion from T to A at nucleotide 2549 was found in polynucleotide encoding Min compared to wild type polynucleotide (page 669, 2nd column, last paragraph). This Min-specific mutation converts codon 850 from a leucine to a stop codon. Thus, the teachings of Su et al. anticipate the limitations of claims 5 and 15.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS